

## **REMARKS**

### **The Amendments**

The claims are amended to specify the pH range and to specify the propellant-free nature of the compositions. The claims are further amended in a non-substantive manner so that they are in a form more customary to US practice.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

### **The First Rejection under 35 U.S.C. §103**

The rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-93 under 35 U.S.C. §103 as being obvious over Freund (DE 19653969, as translated by U.S. 2001/0008632 “Freund ‘632”) in view of Freund (WO 97/01329, as translated by US 6,491,897, “Freund ‘897”), is respectfully traversed.

Applicants previously submitted evidence of the unexpected advantage and nonobviousness of the claimed invention. The evidence demonstrates the nexus between the combination of lower EDTA-content with lower pH and the advantageous absence of spray anomalies. Table 1 of Freund ‘632 shows tests for determining spray anomalies when the EDTA content is modified. Initially, it should be pointed out that Table 1 of Freund ‘632 relates to ipratropium bromide solutions at 3.4 pH (see para. 0048 of Freund ‘632), not tiotropium salt solutions in the claimed pH range. In any event, one of ordinary skill in the art observing the trend in Table 1 of Freund ‘632 – and not having the benefit of applicants’ inventive contribution showing the advantage of combining lower EDTA and lower pH – could not have expected from the reference that a tiotropium bromide solution at pH 2.5 – 3.0 and a lower EDTA amount would lead to less occurrence of spray anomalies. (For the disclosure of applicants’ advantage, see, e.g., page 3, line 19, to page 4, line 7, of applicants’ specification, noting that WO 98/27959 corresponds to Freund ‘632.) To the contrary, Table 1 of Freund ‘632 shows that anomalies occur when the lower amounts of EDTA tested by Freund were used. Only at the higher

amounts, i.e., 50 mg/100 ml and higher, are anomalies avoided. The table in para. 0051 of Freund '632 further evidences that an EDTA amount of 50 mg/100 ml or more is being taught by Freund '632. That applicants' evidence shows avoidance of anomalies at lower pH and lower EDTA amount, i.e., up to and including 25 mg/100 ml is, thus, unexpected in view of Freund '632 and convincing proof of the nonobviousness of the invention as currently claimed.

Freund '632 provides no suggestion that, combining the lower pH and lower EDTA amount, an advantageous avoidance of spray anomalies can be achieved. Freund '632 explicitly teaches a general pH range of 3.2 to 3.4 (page 3, para. 0055) and gives no hint of any advantage for using a lower pH. Freund '632, thus, certainly fails to teach compositions with a pH "of from 2.5 to 3.0." Freund '632 further fails to teach any advantage for a lower sodium edetate amount, as recited in the instant claims. Despite the general disclosure in Freund '632 (para. 0013) that amounts from 10 to 1000 mg/100ml Na-EDTA can be used, the data as discussed above shows a failure to appreciate that amounts lower than 50 mg/100 ml could be used (when combined with the lower pH) to avoid anomalies.

The combination of the broad teaching in Freund '897 that propellant-free aerosol compositions with a pH to between 2.0 and 7.0 can be prepared also fails to provide any expectation from the prior art that, combining the lower pH and lower EDTA amount as currently claimed, an advantageous avoidance of spray anomalies can be achieved. Thus, the combination of the Freund '632 and Freund '897 fails to refute applicants' showing of nonobviousness and, in light of said showing, fails to render the claimed invention obvious.

Consideration of the evidence on the record as a whole – i.e., the data in Freund '632 and the data previously submitted by applicants – shows that applicants have discovered specific conditions which lead to advantages that could not have been expected from the prior art. It is alleged in the Office action that the evidence of record is not commensurate in scope with the claims because the data in Table 1 of Freund '632 shows no tests with compositions of 10 or 25 mg/100ml sodium edetate. This allegation, however, fails to consider all the evidence of record in combination. Applicants have provided evidence showing the advantageous avoidance of anomalies for 10 and 25 mg/100ml sodium edetate compositions within the claimed pH range. In determining obviousness, all evidence of record must be considered for what it reasonably

conveys to one of ordinary skill in the art. One of ordinary skill in the art looking at the Freund '632 data and the general disclosures in both Freund references could never have reasonably considered that compositions of 10 or 25 mg/100ml sodium edetate within the pH range of 2.5 – 3.0 would provide any advantage. The data must be considered together, rather than as separately addressed in the Office action. The Office action further alleges that the data is not convincing of the advantages of the claimed invention because it shows that some embodiments outside the claimed scope also have an advantage. Applicants urge that this allegation is not relevant. All the data considered as a whole shows that the embodiments within the claimed scope of pH and Na-EDTA content show advantages which could not have been expected from what the prior art teaches. It is this unexpected result that supports nonobviousness. Further, the data are not inconsistent with applicants' allegations. At each given pH value where a range of Na-EDTA content is tested, the number of actuations having deviations is always less for the embodiments within the claimed scope (i.e., at 10 or 25 mg/100ml Na-EDTA) compared to the embodiments at 50 mg/100ml Na-EDTA. In view of the teachings from Table 1 of Freund '632, these results could in no way have been expected by one of ordinary skill in the art. For these reasons, applicants maintain their position that the evidence of record provide a clear and convincing case for the nonobviousness of the claimed invention.

As a further basis for nonobviousness, applicants urge that there is not a convincing reason why one of ordinary skill in the art would combine the teaching of Freund '897 with Freund '632 to arrive at a composition according to the claimed invention. Freund '897 does not provide any particular reason for a person of ordinary skill in the art to controvert the express teachings in Freund '632 that its compositions should be in the pH range of 3.2-3.4. The claims and examples in Freund '897 are directed to steroids, either flunisolide hemihydrate or budesonide, and not to tiotropium salts. The pH values exemplified for the steroid compositions in the Freund '897 examples range from 3.2-7.0 (see Tables II, III and IV). Moreover, tiotropium bromide is only mentioned once in a general list in the '897 patent (see column 2, lines 8-9) without any guidance as to the specific dependence of tiotropium salt stability on pH or EDTA content. The differences between the Freund '897 compositions and the Freund '632 compositions are such that one of ordinary skill in the art would not have had a reason to adjust

the pH taught for the Freund '632 by the teachings regarding pH in Freund '897 which relate to distinct compositions.

The cited prior art as a whole fails to provide any valid reason why one of ordinary skill in the art would modify the teachings of Freund '632 in the manner necessary to arrive at the claimed invention and/or achieve the unexpected advantages of the claimed invention. Even if the prior art teachings are combined, they merely provide broad ranges which give no hint to the advantageous selection which forms the basis of the claimed invention. Further, the broad pH range recited in the secondary reference gives no basis for one of ordinary skill in the art to modify the specific 3.2 - 3.4 range explicitly required by Freund '632. There would be no rational reason for one of ordinary skill in the art to modify the Freund '632 compositions based on broad teachings in references related to different types of compositions when Freund '632 gives an explicit teaching for the pH, specifically optimized for its particular compositions. Contrary to the allegation in the Office action and citation of *In re Aller*, Freund '632 does not disclose general conditions encompassing the claimed compositions since one of ordinary skill in the art would have to modify Freund '632 outside its disclosed pH range to arrive at the claimed invention and there is no convincing reason on the record why one of ordinary skill in the art would do so. Rejections on obviousness must be based on some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness (see, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-41, 82 USPQ2d 82 USPQ2d 1385, 1396 (2007); *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); and MPEP § 2141) and such is not provided on the record here.

For all of the above reasons, the cited references taken alone or in combination do not teach, suggest, or make obvious the present invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

### **The Second Rejection under 35 U.S.C. §103**

The rejection of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-93 under 35 U.S.C. §103 as being obvious over Jager (WO 94/13262) in view of Bozong (DE 19921693 as

evidenced by US Patent 6,433,027), is respectfully traversed.

Applicants previously submitted arguments for traversing this ground of rejection primarily based on the non-relevance of this prior art to “propellant-free” compositions. The Office action correctly pointed out that the claims failed to require “propellant-free” compositions. The claims have been amended to make clear that the compositions are “propellant-free.” Thus, it is urged that the basis for withdrawing the rejection is now clear. However, the previous arguments are repeated below for the record.

Jager cannot form the basis for an obviousness rejection because it teaches away from the presently claimed invention. For example, Jager is directed to pharmaceutical solutions containing hydrofluorocarbon (HFC) propellants, whereas the presently claimed invention is directed to specific propellant-free inhalable formulations. In Jager, the preferred propellants used are HFA 227 and HFA 134a. One of skill in the art would not look to propellant-containing formulations for guidance in preparing propellant-free formulations. Moreover, Jager does not exemplify a formulation comprising tiotropium bromide, a solvent and an acid, where the formulation has a pH range of 2.0-3.0 and spray anomalies are reduced with low levels of edetic acid or edetic acid salt.

Bozung, on the other hand, does not disclose or teach the invention as recited in pending claims, specifically with regard to the stability of tiotropium salts in the pH range of 2.0-3.0 and reduction of spray anomalies with low levels of edetic acid or edetic acid salt. In fact, Bozung teaches in one instance (see Table on column 7, lines 20-31) that the pH of its formulation is at a pH of about 3.4. Moreover, Bozung is silent with respect to the specific dependence of tiotropium salt stability on pH and provides no motivation to leave the disclosed pH range of about 3.4. In contrast, the present claims recite that the pharmaceutical preparation of a tiotropium salt has a lower pH limit of 2.5 and an upper pH limit of 3.0.

Additionally, the combined teachings of Jager and Bozung do not form the basis for an obvious rejection because Jager is not relevant art to the presently claimed invention (propellant versus propellant-free solutions) and because both Jager and Bozung are missing key elements of the claimed invention – edetic acid concentration and its affects on spray anomalies and pH (stability). See also the discussion of the unexpected advantages of the claimed invention above.

Based on the claim amendments and arguments made herein, applicants request reconsideration and withdrawal of this rejection.

**The Third Rejection under 35 U.S.C. §103**

The rejection of claims 38-49, 51-52, 81-92, 94 and 95 under 35 U.S.C. §103, as being obvious over Freund (apparently both Freund '632 and '897 discussed above) or alternatively over Jager in view of Bozung, both as applied to claims listed above, and both further in view of Weston (WO 91/14468).

The discussions of the Freund references and the Jager and Bozung references from above is incorporated by reference. To summarize, neither of these combinations of references, when viewed in light of the evidence of record, render the claimed compositions obvious to one of ordinary skill in the art. Weston teaches a particular type of inhaler and is relied upon merely to suggest that the compositions of the primary references or compositions obvious therefrom could be administered using such an inhaler.\

Such a combination, however, would not result in or suggest the invention of these claims because the primary references fail to render the claimed compositions obvious. Using compositions rendered obvious by the primary references in the Weston inhaler will not result in the claimed invention because the compositions would be distinct. Weston provides no teachings which make up for the above-discussed deficiencies of the primary references.

For all of the above reasons, applicants also request reconsideration and withdrawal of this rejection.

### **The Provisional Obviousness-type Double Patenting Rejections**

The provisional rejections of claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 for obviousness-type double patenting over claims of co-pending applications:

- (1) 11/068,134 (US 20050147564);
- (2) 10/392,558 (US 20040019073);
- (3) 12/201,149 (US 20090088408); and
- (4) 11/006,940 (US 20050148562);

are respectfully traversed.

According to MPEP 804(I)(B)(1), “if a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.” All of the above-listed copending applications have effective US filing dates after the earliest effective filing date of the present application and qualify as “later-filed” applications. Should these double patenting rejections be the only remaining rejections in this application, the practice requires that they be withdrawn. Thus, for example, terminal disclaimers are not necessary for allowance of the present claims.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/John A. Sopp/

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John A. Sopp, Reg. No. 33,103  
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO  
& BRANIGAN, P.C.  
Arlington Courthouse Plaza 1, Suite 1400  
2200 Clarendon Boulevard  
Arlington, Virginia 22201  
Telephone: (703) 243-6333  
Facsimile: (703) 243-6410

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